REMARKS

Claims 1-11 have been examined, claims 1-4, 6-7, and 9-11 are amended, and claims 5 and 8 are cancelled herein. Accordingly, claims 1-4, 6, 7, and 9-11 are now pending in the application. Reconsideration of all outstanding objections and rejections and reexamination is requested.

Claims 7-11 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description. Claim 7 has been amended to remove terms such as "first biological tissue sample" and "sub-samples" pointed out by the examiner and claims 9 and 10 have been amended to remove such terms as "image pixel". All terms used in the amended claims are also used in the detailed description.

Paragraph [42] has been amended to better describe the operation of the embodiments. No new matter is introduced because the material was taken from the MultiVIS paper incorporated by reference in paragraph [21] to describe mapping of both volume image data and other types of data, such as object identity data, onto a single x,y,z coordinate space.

Claims 1-6 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Heppelmann et al. in view of Cole et al., Farr et al., and Emmert-Buck et al.

One embodiment of the present invention, as recited for example in claims 1, 4, 7, and 11, includes the steps cutting histologically thin serial sections of a biological sample, constructing a multidimensional morphological matrix of image data based on the serial samples, incising a grid pattern on serial samples to form a set of incised section samples, and indexing the incised section samples with indices indicating the location of the incised sections samples in the multidimensional morphological matrix of image data.

Each indexed incised section sample is then analyzed to obtain biological data characterizing the indexed incised section sample. This biological data is then spatially mapped onto the multidimensional morphological spatial matrix to superimpose the biological data upon volume image data correlated to indices associated with each indexed incised section sample.

Heppelmann discloses two different techniques for three-dimensional reconstruction of extended fine tissue structures: a re-embedding technique and a serial section-ESI technique. It also describes true-to-scale three-dimensional reconstructions.

In the re-embedding technique, the extended fine tissue structure is cut into semi-thin serial sections and the semi-thin sections are examined under oil immersion and photographed. If a semi-thin section is selected for ultra-structural examination then the semi-thin section is re-

embedded and converted into a series of ultra-thin sections for viewing the ultra-structural detail of the tissue within that section. Heppelmann, page 164, Re-embedding technique, first and second paragraphs.

Further, in the serial section-ESI technique, a set of serial sections is cut and analyzed utilizing ESI. Heppelmann mentions cutting a complete set of alternate semi- and ultra-thin sections of a tissue block. However, all of these sections are then mounted, in their entirety, in sequence on a mesh transmission grid and imaged using ESI. *Id.*, page 165, first paragraph.

The result of the Heppelmann product is a series of images of the sections, as depicted on the left side of Fig. 4, which can be used to form a 3-D reconstruction depicted on the right side of Fig. 4. The serial sections on the left side of Fig. 4 form the x,y planes of the 3-D structure and the location of the sections in the 3-D structure is indicated by a z coordinate.

The reference Cole teaches the use of histologically cut serial sections to precisely identify specific tumor cells within the prostate gland which are then selected and excised for microarray analysis of expression activity.

In Cole, a 3-D representation of a prostate gland is formed by stacking whole-mount transverse sections cut from the sample. Each serial section may be viewed and is annotated to show the locations where cell populations have been dissected and analyzed. By interactively clicking on these annotations the user can query a database for data related to a selected cell population. In Cole the selection of the cells to be analyzed occurs prior to the dissection of those cells, and those cells are a specific subset of the cells that make up the entirety of the prostate tissue contained in the series of transverse sections.

The Farr reference merely shows that one can study specific cells for a set of several biological parameters at once and includes graphs depicting the relative concentration of a specific chemical as a function of various concentrations of another chemical.

Emmert-Buck discloses placing a thin transparent film over a tissue section, visualizing the tissue section microscopically, and selectively adhering the cells of interest within the tissue section to the film with a fixed-position, short-duration, focused pulse from an infrared laser. The adhered section is removed from the serial section providing the image data.

The examiner states that Heppelmann describes performing three dimensional reconstructions with graphical techniques and computer-aided methods featuring a spatial matrix of image data as seen in Fig. 4. It is further stated that it would have been obvious to utilize improved methods of comparison of multidimensional graphic data expression representation to microscopy data, as stated in Cole, via three-dimensional histological techniques to increase understanding of

complex morphological structures as stated by Heppelmann and using simple and precision tissue extraction with laser capture microdissection that minimizes contamination, as stated by Emmert-Buck, and displaying the gene expression data in easy-to-read-three-dimensional graphs as shown by Farr because these exact and efficient techniques would improve accuracy and visual representation for easy interpretation of correlations between the two types of data available to scientists at the time of the invention.

It is also stated that Heppelmann describes the sections were mounted on a sequence of grids which is reasonably interpreted to be indexed as it has grids with each individual sample placed in known locations as stated in claims 1, 4, and 5.

This rejection is respectfully traversed for the following reasons.

As set forth above, none of the references disclose the steps recited in claim 1, 4, 7, and 11. The establishment of a *prima facie* case of obviousness requires that all the claim limitations must be taught or suggested by the prior art. MPEP §2143.03.

The steps of incising a grid pattern on a serial section to form a set of incised section samples and assigning indices to the incised section samples to indicate the position of each indexed incised section sample in the multidimensional morphological matrix of image data is not disclosed or suggested in any of the references.

The grid mentioned in Heppelmann is not relevant to teaching the claimed step of incising a grid pattern. Heppelmann states: "The sections were mounted in sequence on Formvar-created 200-hexagonal mesh ultrahigh transmission grids (Gilder grids, London) and stained with uranyl acetate and lead citrate." Thus the term "grid" used in Heppelmann refers to the mesh-like structure of the substrate utilized to mount the sections and is not related to incising the sections themselves into a grid pattern or assigning coordinates to the sections.

In the Heppelmann re-embedding technique an entire selected semi-thin section is re-embedded and subjected to ultra-structural analysis. In the serial section-ESI technique entire ultra-thin sections are imaged. There are no steps of incising a serial section into a grid and assigning indices to the incised section samples in either Heppelmann technique.

In Cole, selected cell populations are dissected from the serial sections for analysis. There is no step of incising a serial section into a grid and assigning indices to the incised section samples.

In Emmert-Buck a sample is viewed and selected cells of interest are adhered to a film and dissected from the sample. There are no steps of incising a serial section into a grid and assigning indices to the incised section samples the Emmert-Buck technique.

Accordingly, none of the references disclose the steps recited in claims 1, 4, 7 and 11 and a *prima facie* case of obviousness has not been established.

Further, the establishment of a *prima facie* case of obviousness requires that the claimed combination cannot change the principle of operation of the primary reference or render the reference inoperable for its intended purpose. MPEP §2143.01.

The fundamental principal of operation in the re-embedding technique of Heppelmann, the 3-D model of Cole, and the laser capture micro-dissection of Emmert-Buck is that an area of interest is selected from a section being viewed for further analysis.

In contrast, the method recited in claims 1, 4, 7, and 11 works on a fundamentally different principle of operation in that a grid is incised across the serial sections without any selection by a viewer, and the incised sections are further analyzed. This allows selection to occur at anytime and the complete data set is available to be mapped onto the multidimensional image matrix. For example, in Cole if an investigator needed data at a location that had not been previously selected, dissected, and analyzed it would be necessary go back and dissect another cell population for analysis which might not be possible. Thus, the present system lends itself to a survey approach rather than a directed selection approach.

Thus, the proposed combination would change the principle of operation of the primary reference and render it inoperable. If the serial section of Heppelmann were incised into a grid pattern it could not be used for the next step of ultra-structural analysis since the structure of the serial section would have been destroyed.

Accordingly, a prima facie case of obviousness has not been established.

Claims 1 and 4 recited additional steps of cutting histologically thin sections of biological tissue to form two sets of alternating serial sections of the biological tissue. Image data from the first set of alternating serial sections is mapped onto a tissue space coordinate system to construct a multidimensional morphological tissue space matrix of image data.

Each serial section of the second set of alternating serial sections is incised into a grid pattern to create a set of incised section samples for each serial section in the second set of alternating serial sections to form a set of indexed incised section samples. Each of these incised section samples is then associated with a unique set of indices that indicate a tissue space coordinate of the sample in the morphological tissue space matrix.

None of these steps is disclosed in the cited references. In the re-embedding technique of Heppelmann a selected semi-thin section is re-embedded for ultra-structural analysis, in Cole cell populations are dissected from the same cross section that is viewed, with locations of

excised cell populations annotated on the image of the cross-section, in Emmert-Buck cells are selectively adhered from the section being viewed.

The serial section-ESI technique of Heppelmann discloses cutting a set of serial sections, which may alternate as semi- and ultra-thin sections, mounting the sections sequentially on a mesh grid, and imaging the sections using ESI.

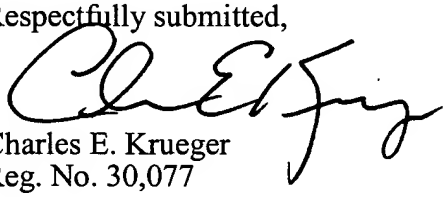
Thus there is no disclosure of the claimed steps of producing alternate sets of serial sections, using the first set to obtain image data, excising a grid pattern on the second set and assigning indices to the incised section samples indicating tissue space coordinates. Accordingly, a *prima facie* case of obviousness has not been established.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (925) 944-3320.

Respectfully submitted,



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